## REMARKS

At the outset, Applicants thank Examiners Li and Nguyen for their time in conducting an interview on July 18, 2005.

*Claim amendments*

Claims 1, 2, 11, 16, 17, and 20 have been amended to recite an "an immune response" instead of "a cellular immune response". Claim 5 has also been amended to recite "thereby inducing an immune response specific to the immunodeficiency viral protein". Support for these amendments is found, for example, at page 10, lines 27-29 and page 38, lines 1-8.

Claims 2 and 17 have been amended to recite Pol, gp41, and Gag-Pol fusion protein in addition to Gag. Furthermore, claims 5, 11, 20, and 33 have been amended to recite specific immunodeficiency viral proteins. Support for these amendments is found, for example, at page 17, lines 1-12.

Claims 9, 24, 37 and 39 have been amended to recite "intramuscularly or intradermally" and "naked". Support for these amendments is found, for example, at Example 9 on page 57, and on page 13, lines 8-25, respectively.

New claims 62-66 have been added. Support is found throughout the specification.

No new matter has been added by any of the aforementioned amendments.

*Rejections under 35 U.S.C. § 112, first paragraph – written description*

Claims 1-5, 7, 9, 11-20, 24, 26, 28-33, 37, 39, and 41-45 stand newly rejected under 35 U.S.C. § 112, first paragraph, for failing to comply to the written description requirement.

As noted in the interview, the Office explained that the rejection focused solely on the claim language reciting "a part of any of them." Applicants, as noted during the interview, point out that their specification, for example, at page 22, line 2 through page 23, line 7, provides specific examplary parts of a Pol, gp41, Tat, Rev, Vpu, Vpx, Vpr, Vif, Nef, Gag protein, or a Gag-Pol fusion protein. The specification unambiguously informs skilled artisans of the parts of these proteins. The claim term at issue here is not one that ordinarily skilled artisans would easily miscomprehend. Moreover, the Office supplies no substantial evidence showing that skilled artisans would be unable to understand the specification's teachings. In sum, Applicants' specification shows that the inventors possessed the claimed invention at the time of filing and the written description rejection should therefore be withdrawn.

Turning to the Office's treatment of the Matano reference, Applicants note that this reference does not support the present written description rejection. Applicants respectfully point out that it appears that the Office has misconstrued the Matano teachings. Matano does not stand for the premise that SeV-Tat cannot induce a protective cellular immune response as suggested by the Office. Matano teaches that a tat-specific immune response was in fact induced though Tat is less effective than Gag.

In fact, Matano expressly qualifies the findings, noting that "these results do not deny the potential of Tat-based AIDS vaccines but suggest the importance of the careful selection of antigens for the development of an AIDS vaccine (see, Matano, sentence bridging p. 1392 and p. 1393, last paragraph)." Therefore, Matano evidences that immunodeficiency viral proteins other than Gag can be used in the instant invention.

*Rejections under 35 U.S.C. § 112, first paragraph – enablement*

Claims 1-5, 7, 9, 16-20, 24, 26, 28-33, 37, 39, and 41-45 stand newly rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement.

*Type of Sendai viral vector*

The Office alleges that, as the type of Sendai viral vector, the specification is enabling for only V(-)SeV. The Office suggests that the experimental findings disclosed in Applicants' specification are limited to V(-) SeV, and, as such, fail to enable the broader category of SeV vectors in general. Indeed, the specification, for example, at page 18, lines 27-28, makes clear that both wild-type and mutated SeV vector are useful in the claimed invention. Moreover, the Office's reliance on Applicants' subsequent publication of a mutated SeV vector is irrelevant to the enablement question. It is the sufficiency of Applicants' present specification on which an enablement inquiry is based, not Applicants' publication record. Indeed, the burden is on the Patent Office to establish a reasonable basis to question enablement in view of Applicants' specification. Moreover, for the Office to sustain a rejection on the grounds of enablement, it must

provide evidence that the claimed method could not be performed without undue experimentation.

No evidence or line of reasoning has been presented to contradict Applicants assertion that other SeV embodiments, including those of withdrawn claims 46-61 directed to an F(-) or env(-) SeV as well as those directed to an SeV lacking the M, F, and/or HIN genes (see specification at page 19, lines 28-29), are capable of inducing antigen-specific immune responses, either in vitro or in vivo. Accordingly, the Office has failed to meet its burden of proof and this basis of the rejection should be withdrawn.

Moreover, with respect to the breadth of a claim relative to enablement, the only relevant concern should be whether the scope of enablement provided by the disclosure is commensurate with the scope of protection sought by the claims. M.P.E.P. 2164.08; *In re Moore,* 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Importantly, the scope of enablement need only bear a "reasonable correlation" to the scope of the claims. See, for example, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art – in view of the level of skill, state of the art, and information in the specification – would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement for other members of the claimed genus should only be required where adequate reasons are advanced by the Office to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

In this case, the Office has not only failed to provide any substantial grounds for doubting Applicants' assertions and findings but has also failed to advance adequate reasons as to why, in view of the positive findings with respect to the V(-)SeV, a person skilled in the art could not extrapolate the disclosed method to other SeV embodiments, either comprising intact SeV or involving the attenuation or inactivation of other SeV genes.

To demonstrate that SeV other than V(-)SeV is enabled, Applicants direct the Office's attention to the following references (copies enclosed): Matano et al., AIDS, 2003 Jun 13;17(9) 1392-4; Matano et al., J. Exp. Med. 2004, 199, 12, 1709-18; Takeda et al., J. Virology 2003, 77, 17, 9710-5; and Kato et al., Vaccine, 2005, 23, 24;3166-73 (PubMed abstract). Matano (AIDS) discloses use of a V(+)SeV (intact SeV). Matano (J. Exp. Med.), Takeda (J. Virology), and Kato (Vaccine) each disclose the use of F(-)SeV as an AIDS vaccine. In view of the teachings of these references, the Office's concerns regarding the vaccine effects of additional SeV vectors and V(+)SeV, in particular, is unwarranted.

*Type of immunodeficiency viral protein*

As an initial matter, applicants note that Gag, Pol, and Env are known structural proteins, Tat and Rev are known regulatory proteins, and Vpu, Vpr, Vif, and Nef are known accessory proteins of immunodeficiency viruses. See, for example, Applicants' specification at p. 21, line 30 to p. 22, line 32. Accordingly, the mere listing of the viral proteins constitutes a constructive reduction to practice of each member of the claimed

genus. Furthermore, the members of the genus share the common characteristic of being candidate vaccine antigens for the construction of an immunodeficiency virus (e.g., SIV, HIV, etc.) vaccine. The Office's own references support this point. For example, the Ouramanov and Hirsch references describe the Gag-Pol fusion protein and the Env protein of SIV as potential vaccine antigens for HIV and AIDS. Likewise, the Boutillon reference describes fragments of the HIV Env, Nef and Gag proteins as CTL-inducing immunogenic viral antigens having vaccine utilities. In addition, Geffen et al. (AIDS Res Hum Retroviruses. 1998 May 1;14(7):579-90; copy enclosed) found the transmembrane glycoprotein gp41 to be an important component in the formulation of a vaccine or for immunotherapeutic approaches to HIV-1 infection. Ensoli et al. (J Biol Regul Homeost Agents. 2000 Jan-Mar;14(1):22-6; copy enclosed) found that immunization with the HIV Tat protein induced specific humoral and cellular immune responses, including Tat-specific proliferation, CTLs, and TNF-alpha production, and, upon challenge, was capable of controlling the acute phase of infection in nonhuman primates. Likewise, Leung et al. (Virology, March 1, 2000, 268(1): 94-103; copy enclosed) demonstrate that a single simultaneous inoculation of constructs expressing SIV Gag, Pol, Env, and Nef proteins can induce concomitant humoral and cellular immune responses to these primary viral proteins. In fact, the NIAID's SPIRAT group found that both antibody and cellular immune responses were stimulated by injection of the viral genes, env and rev (NIAID AIDS Agenda, September, 1995). Finally, Ayyavoo (Vaccine. 1998 Nov;16(19):1872-9; copy enclosed) describe effective genetic HIV vaccines, which include accessory genes

vif, vpr, vpu and nef, that effectively induce both humoral and cellular responses in mice and the resulting immune response is directly correlated with DNA concentrations delivered and the number of boosts, a strategy that finds utility the development of an effective, safe DNA vaccine for any pathogen.

To further support that any immunodeficiency viral proteins can be used, Applicants submit Kano et al. (Jpn. J. Infect. Dis., 2002, 55, 59-60; copy enclosed). This reference teaches induction of HIV-1-specific antibodies in mice vaccinated with SeV/HIV-1 Env.

Finally, regarding the term a part of the protein, the specification provides specific examples of and/or guidance as to selection of protein fragments. For example, processed proteins and epitopes are exemplified as a part of the protein at page 22, line 2 to page 23, line 7. It is well known in the art that such processed proteins and epitopes have antigenicity. As for the induction of an epitope-specific immune response, Applicants direct the Office's attention to the following references (copies enclosed): Ciernik et al., J. Immunol. 1996, 156, 2369-75 (PubMed abstract); Ishioka et al., J. Immunol. 1999, 162, 3915-25; Allen et al., J. Virol. 2002, 76, 4108-12; Allen et al., J. Virol. 76, 10507-11; and Subbramanian et al. J. Virol. 2003, 77, 10113-8.

Accordingly, at the time of invention, the claimed immunodeficiency viral proteins constituted a well-recognized class of potential vaccine antigens and, as such, are both sufficiently described and enabled. In fact, the Office Action states at p. 24, lines 6-9, that the prior art teachings "would reasonably suggest to the skilled artisan that one can

use different types of viral vectors for expressing a [sic] HIV/SIV protein and using such for vaccination with a reasonable expectation of success". The Office further admits that "[i]t is well known that certain HIV proteins such as the gag and gag-pol fusion could induce a long-lasting humoral and cellular response" (OA, p. 23, lines 19-20). Accordingly, the requisite clear line of reasoning is not only noticeably absent but also in conflict with the reasoning set forth by the Office in determining obviousness.

*Routes of administration*

The Office alleges that the specification fails to teach routes of administration other than an intradermal gene gun approach. Applicants disagree. The specification describes intramuscular inoculation as well as administration using an intradermal gene gun (see Example 9). To expedite prosecution, Applicants have amended claims 9, 24, 37, and 39 to limit the route of administration to intramuscular or intradermal inoculation.

*DNA vaccine*

The Office asserts that the specification fails to teach DNA vectors other than a plasmid. To expedite prosecution, Applicants have amended "DNA" to "naked DNA" in claims 9, 24, 37, and 39.

The Office additionally notes that it is unlikely a DNA vector, particularly a plasmid vector, could carry the entire genome of SHIV. The Office's concern is misplaced. HIV/SIV molecular clone plasmids are well known in the art (see Adachi et al., J. Virology 1986, 59, 2, 284-91; copy enclosed). Such plasmids express all of the encoded viral proteins to produce infective viral particles. Furthermore, such plasmid

vectors are commercially available (see, for example, Clontech online catalog and U.S. Patent No. 5,766,945; copies enclosed).

*Rejections under 35 U.S.C. § 112, second paragraph*

Claims 5, 7, 9, 20, 24, 26, 28-33, 37, 39, and 41-45 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite. In particular, the Office has pointed out that the subject of the intranasal administration or DNA plasmid inoculation is missing. To expedite prosecution, Applicants have amended claims 5, 7, 9, 20, 24, 33, 37, and 39 to include specific reference to the "subject" or "animal" being treated and this rejection should therefore be withdrawn.

*Rejections under 35 U.S.C. § 102(f)*

Claims 1-4 and 16-19 were rejected under 35 U.S.C. § 102(f) on the grounds that these claims are drawn to subject matter that is encompassed by claims 1, 4, 5, and 13 of copending application 09/728,207. As pointed out during the interview and acknowledged by Examiner Nguyen, this application fails to teach the claimed invention and therefore this rejection should be withdrawn.

*Rejections under 35 U.S.C. § 103*

Claims 1-4 and 16-19 were provisionally rejected under 35 USC 103(a) as being obvious over Nagai et al. in view of Nagai et al. (the '207 application) in view of Yu and

Hirsch. According to the Office Action, Nagai et al. constitutes prior art only under 35 USC 102(e). Applicants will address this rejection, if appropriate, upon an indication of allowable subject matter by filing a statement indicating that the applications were, at the time this application was filed, commonly owned.

Claims 1-3, 5, 7, 9, 16-18, 20, 24, 26, 28-33, 37, 39, and 41-45 stand rejected under 35 U.S.C. § 103(a) as being obvious over Flanagan et al. (JGV, 1997) in view of Seth et al. (PNAS, 1998), Hurwitz et al. (Vaccine, 1997) and Yu et al. (Genes Cells, 1997) as evidenced by Ourmanov et al. (J. Virol. 2000). Claims 11-13 and 15 stand rejected as unpatentable over Flanagan et al. (JGV, 1997) in view of Yu et al. (Genes Cells, 1997) and Kast et al. (J. Immunol. 1988). And claim 14 stands rejected as unpatentable over Flanagan et al. (JGV, 1997) in view of Yu et al. (Genes Cells, 1997) and Kast et al. (J. Immunol. 1988), further in view of Boutillon et al. (U.S. Patent No. 6,015,564). For the following reasons, each of these rejections should be withdrawn.

Flanagan teaches an adenovirus expressing SIV gag. Seth and Ourmanov teach a vaccinia virus vector expressing gag-pol fusion (or Env) polypeptides. Adenoviruses and vaccinia viruses are clearly not Sendai viruses and are therefore not interchangeable, as the Office Action assumes. The Office fails to provide a single reason supporting this assumption, and on this basis alone the § 103 rejections should be withdrawn.

Applicants also reiterate that the specific combination described and claimed has distinct advantages that make it superior to other immunodeficiency virus vaccines. For example, the recombinant Sendai virus vaccine vector as claimed: (a) is able to

remarkably decrease viral loads in chronic phase (see, for example, the Specification, at p. 3, lines 25 – 28) and yields remarkable infection protection using only a single antigen (see, for example, the Specification, at p. 4, lines 34 – 36); (b) is less cytotoxic and yields antigen expression levels that are higher in mammalian cells (see, for example, the Specification, at p. 3, lines 35 – 36); (c) is able to induce antigen specific cellular immune responses and induce systemic mucosal immunity *in vivo* using lower dosages (see, for example, the Specification, at p. 4, lines 27 – 29 and p. 5, lines 21 – 23); and (d) is non-pathogenic to humans and relatively safe, having a localized and well-controlled antigen expression pattern (see, for example, the Specification, at p. 5, lines 15 – 20 and p. 8, lines 5 – 7). In other words, the Sendai virus is unexpectedly superior to prior art vaccine vectors, such as adenovirus and vaccinia virus, in that, due to its high transgene expression level and high infectivity of the nasal cavity (i.e., mucosal tissues), a small dose can produce substantial, protective, and antigen-specific vaccine response. Accordingly, it appears that the instant rejection is a result of piecemeal analysis and not the result of consideration of the invention as a whole. For this reason too, the suggestion of obviousness is improper.

Applicants further point out that none of the cited references disclose or suggest the use of a recombinant SeV to induce an antigen-specific immune response. In fact, none of the cited reference disclose or suggest the use of a recombinant SeV in a living system. The only reference that even discloses recombinant, foreign gene-carrying SeV is the Yu reference and its teachings are limited to the use of SeV as an *in vitro*

expression vector. There is simply no suggestion anywhere in the Yu reference that a recombinant Sendai virus vector would be suitable for mucosal vaccination against immunodeficiency virus, capable of inducing an antigen specific immune response, particularly in a living system.

Moreover, when considering the Yu reference as a whole, there is clearly no suggestion of using the Sendai virus as a carrier vector for delivering exogenous viral antigens to host cells so as to induce an immune response specific thereto as required by the pending claims.

In addition, neither Kast nor Hurwitz suggest that recombinant, foreign gene-carrying SeV would act in a manner analogous to live SeV and be capable of inducing an immune response specific to an exogenous protein carried thereby, either *in vivo* or *in vitro.*

Furthermore, neither Hurwitz, Yu, nor Kast, the only cited references relevant to Sendai virus, describe it as a suitable delivery vector for vaccine antigens, much less as a suitable vector for mucosal vaccination against an immunodeficiency virus capable of eliciting an antigen-specific immune response as claimed. In fact, contrary to the Office's suggestion, at the time of invention, Sendai virus was not known as delivery vector for exogenous vaccine antigens, nor was it known to be an effective means for mucosal vaccination against infection with a foreign virus.

One skilled would not have been motivated to combine the Hurwitz and Yu teachings as the Office suggests since the resulting combination would not retain the

beneficial properties described by Hurwitz, namely the ability to provide a long lasting effect B-cell as well as CTL response (a property associated with live viruses as compared to attenuated and inactivated viruses such as disclosed by Yu).

Furthermore, neither Hurwitz, Yu, nor Kast disclose or suggest that Sendai virus would be suitable as a vaccine vector, capable of inducing a protective, antigen-specific immune response. In fact, the Kast reference casts doubt on the ability of wild-type Sendai virus to ubiquitously induce a specific CTL response to Sendai viral proteins themselves, noting that the bm14 mouse demonstrated a virus specific CTL response while the bm1 mouse did not. See Kast, p. 3186, col. 2. Likewise, the Yu disclosure casts doubt on the ability of the Sendai virus to express foreign proteins other than gp120, noting the recorded failure of a Sendai virus vector to yield functional luciferase. See Yu, p. 463, col. 2. Taken together, these references indicate that, prior to Applicants pioneering data concerning recombinant SeV as an efficient and efficacious delivery vector for AIDS vaccine antigens, the properties and activities of the Sendai virus were difficult to predict.

Since the findings of Hurwitz relate to the use of live, wild-type, Sendai virus as a vaccine antigen and not as a vaccine vector for the delivery of exogenous antigens, at the time of invention, one skilled in the art could not have reasonably predicted that a recombinant Sendai virus vector could induce an immune response specific to an exogenous immunodeficiency viral protein as required by the instant claims. Accordingly, as one skilled in the art could not have predicted with any reasonable

degree of certainty that a recombinant Sendai viral vector would be successful at inducing a protective, antigen-specific immune response, and therefore be suitable as an immunodeficiency virus vaccine, the suggestion of obviousness is improper.

In sum, for all of the reasons previously made of record in this case and for those reiterated above, Applicants maintain that the Office has failed to establish a prima facie case of obviousness and the section 103 rejections should be withdrawn.

## CONCLUSION

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for three months, to and including July 26, 2005, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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